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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 2860**
Shunichi SHIOZAWA et al.	:	Docket No. 2001-1298A
Serial No. 09/936,989	:	Group Art Unit 1634
Filed October 30, 2001	:	Examiner C. Myers
RHEUMATOID ARTHRITIS GENE AND METHOD FOR DIAGNOSING RHEUMATOID ARTHRITIS	:	

AMENDMENT

Assistant Commissioner for Patents,
Washington, D.C. 20231

Sir:

Responsive to the Official Action dated April 24, 2002, the time for filing thereto being extended for two month in accordance with the Petition for Extension submitted concurrently herewith, please amend the above-identified application as follows.

In the Specification:

Page 1, line 1, delete the entire heading.

between lines 4 and 6, insert the following new heading:

BACKGROUND OF THE INVENTION

line 6, replace the heading with the following new heading:

1. Field of the Invention

line 12, replace the heading with the following new heading:

2. Description of the Related Art

Page 3, line 11, replace the heading with the following new heading:

Summary of the Invention

replace the paragraph beginning at line 12 with the following paragraph:

B1 In order to solve the above-described problems, the present invention provides a cDNA of a disease gene for rheumatoid arthritis, which has the base sequence of SEQ ID NO: 1.

replace the paragraph beginning at line 20 with the following paragraph:

B2 The present invention also provides a DNA fragment, which is a part of such cDNA and necessarily contains the base sequence from 2693rd to 2702nd of SEQ ID NO: 1, a protein expressed by the above disease gene, a peptide which is a part of such protein, and an antibody against such protein.

Page 4, between lines 4 and 6, insert the following:

Brief Description of the Drawing

B3 Figure 1 shows the base sequence of the 2679th to 2952nd bases of the Dbl gene cDNA in its normal form (see bases 2679 to 2952 of SEQ ID NO: 5), the corresponding base sequence of the cDNA of the disease gene of RA (see bases 2679 to 2757 of SEQ ID NO: 1), and the respective amino acid sequences (1 letter notation) encoded by these sequences (see amino acid residues 836 to 860 of SEQ ID NO: 2 and amino acid residues 836 to 925 of SEQ ID NO: 6).

line 6, replace the heading with the following new heading:

Description of the Preferred Embodiments

replace the paragraph beginning at line 9 with the following paragraph:

The cDNA of the disease gene for rheumatoid arthritis of the present invention (hereinafter referred to as "cDNA") is a variant sequence of known protooncogene Dbl cDNA (EMBO J. 7(8): 2463-2473, 1988; GenBank Accession No. X12556) (SEQ ID NO: 5). In the cDNA of the present invention, the sequence on the 3' side of the 2919th base in GenBank/X12556 (SEQ ID NO: 5) is linked to the downstream side of the 2696th base in GenBank/X12556 (SEQ ID NO: 5) to induce a frame shift in amino acid translation (and eliminate bases 2697 to 2919 of SEQ ID NO: 5), creating the sequence shown in SEQ ID NO: 1. Figure 1 shows the base sequence of the 2679th to 2952nd bases of the Dbl gene cDNA in its normal form (see bases 2679 to 2952 of SEQ ID NO: 5), the corresponding base sequence of the cDNA of the disease gene of RA (see bases 2679 to 2757 of SEQ ID NO: 1), and the respective amino acid sequences (1 letter notation) encoded by these sequences (see amino acid residues 836 to 860 of SEQ ID NO: 2 and amino acid residues 836 to 925 of SEQ ID NO: 6).

Page 5, delete lines 1-8 in their entirety.

replace the paragraph beginning at line 25 with the following paragraph:

The DNA fragment of the present invention comprises a portion of the aforesaid cDNA, and necessarily contains the base sequence from 2693rd to 2702nd of SEQ ID NO: 1. In other words, 2693rd to 2702nd of SEQ ID NO: 1 is the underlined sequence in Figure 1, and is a characteristic region, which is not present in normal Dbl gene or its cDNAs. Further, the DNA

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fragment includes both sense and antisense strands. These DNA fragments may be used as probes for genetic diagnosis.

Page 6, replace the paragraph beginning at line 7 with the following paragraph:

The proteins of the present invention are expression products resulting from the RA disease genes of the present invention, and has the amino acid sequence shown in SEQ ID NO: 2. These proteins may be obtained by chemical peptide synthesis method based on the amino

B6 acid sequence provided by the present application, or by recombinant DNA technique using cDNAs provided by the present application. For example, when recombinant DNA technique is used to obtain the proteins, RNA may be prepared by *in vitro* transcription using a vector containing the cDNA of the present invention; using this RNA as a template, the proteins may be obtained by *in vitro* translation. Also, the coding region of the cDNA may be recombined into an appropriate expression vector by any known method, and the recombinant vector obtained may be used to transform *E. coli*., *Bacillus subtilis*, yeast, animal cells or the like, whereby expression of the protein in bulk would be possible using these recombinant cells.

Page 12, replace the paragraph beginning at line 15 with the following paragraph:

In order to compare the cDNAs between of Dbl genes, cDNA was synthesized by reverse transcription using RT-PCR kit (Perkin Elmer Inc.) from the total RNA obtained from

B7 peripheral blood of RA disease patients collected using Isogen agent (Nippongene Co. Ltd.), and dissolved in 20μl of sterilized water. Furthermore, primers (SEQ ID NOs: 3 and 4) were prepared using the Dbl cDNA sequence (Genbank Accession No. X12556) (Amersham Pharmacia), and part of the Dbl cDNA sequence was isolated by the PCR method. The

composition of the reaction solution for PCR was: 10 pmol each of forward primer (SEQ ID NO: 3) and reverse primer (SEQ ID NO: 4), approximately 0.1μg of template DNA, 2.5μl of LA-PCR buffer (Takara Shuzo Co. Ltd.), 4.0μl of 2.5mM dNTP Mix, 0.25μl of LA Taq enzyme (Takara Shuzo Co. Ltd.) and 2.5μl of 25mM $MgCl_2$ mixed, after which sterilized water was added to obtain a total volume of 25μl. The reaction was performed in a thermal cycler (PTC-200) of MJ Research by repeating 35 cycles of the process of heat denaturation at 94°C for 30 seconds, primer annealing at 52°C for 30 seconds and extension at 72°C for 2 minutes. The PCR products were subjected to electrophoresis of conventional methods, in TAE buffer solution using 1% Agarose L (Nippongene Co. Ltd.) gel and DNA molecular weight markers (200bp ladder) by Promega Co., to confirm the amplified bands. As a result, it was found that the size of normal DNA was 660bp while the size of DNA chain from some patients were distinctly shorter (approximately 440bp).

Page 14, line 6, delete the entire heading.

replace the paragraph beginning at line 7 with the following paragraph:

As described in detail above, the present invention provides a cDNA of a disease gene for rheumatoid arthritis occurring in human chromosome X. This invention enables the easy and reliable diagnosis of rheumatoid arthritis. Furthermore, this invention is useful for the development of novel treatment and therapeutic agents for rheumatoid arthritis.

In the Abstract:

Page 16, line 1, replace the heading with the following new heading:

ABSTRACT OF THE DISCLOSURE

In the Sequence Listing:

Please replace the Sequence Listing of record pages 1-2 with the attached substitute Sequence Listing consisting of pages 1-17.

In the Claims:

Above claim 1, insert the following:

What is claimed is:

Kindly cancel claims 2 and 9 without prejudice.

Please amend the claims as follows.

1. (Amended) A cDNA of a disease gene for rheumatoid arthritis, which comprises the base sequence of SEQ ID NO: 1.

3. (Twice Amended) A DNA fragment which comprises the base sequence of a part of SEQ ID NO: 1, and necessarily contains the base sequence from 2693rd to 2702nd of SEQ ID NO: 1.

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7. (Twice Amended) A method for diagnosing rheumatoid arthritis, said method comprising detecting an mRNA from the cDNA of claim 1, in a biological specimen.

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11. (Amended) A method for diagnosing rheumatoid arthritis, said method comprising detecting the protein of claim 4, in a biological specimen.

Kindly add the following new claims.

12. A polynucleotide comprising the base sequence of SEQ ID NO: 1.

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13. A polynucleotide comprising the base sequence of a part of SEQ ID NO: 1, and necessarily contains the base sequence from 2693rd to 2702nd of SEQ ID NO: 1.

14. The polynucleotide according to claim 13, which consists of the base sequence from 2693rd to 2702nd of SEQ ID NO: 1.

15. A method for diagnosing rheumatoid arthritis, said method comprising detecting the DNA fragment of claim 3, in a biological specimen.

16. A method for diagnosing rheumatoid arthritis, said method comprising detecting the polynucleotide of claim 12, in a biological specimen.

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17. A method for diagnosing rheumatoid arthritis, said method comprising detecting the polynucleotide of claim 13, in a biological specimen.

18. A method for diagnosing rheumatoid arthritis, said method comprising detecting the polynucleotide of claim 14, in a biological specimen.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

With regard to the Restriction Requirement, Applicants hereby again affirm the election of Group I, claims 1-3 and 9. It is noted that the election was made by the Applicants while retaining their right to file a Divisional Application directed to the non-elected subject matter with the protection afforded by 35 USC § 121.

Claims 4-6, 8, 10 and 11, directed to non-elected subject matter, remain in the application. It is again requested that they be permitted to remain in a dormant condition pending the filing of a divisional application. Applicants note that claim 7, also directed to non-elected subject matter, has been amended for possible rejoinder under *In re Ochiai* and *In re Brower*. Applicants request that this claim as well as new claims 15-18 be examined upon the allowance of the elected claims.

Applicants have submitted a revised Sequence Listing in both paper and computer readable form as required by 37 C.F.R. 1.821(c) and (e). Amendments directing its entry into the

specification have also been incorporated herein. The content of the paper and computer readable copies are the same and no new matter has been added.

The revised Sequence Listing incorporates changes which are clearly supported by the specification as originally filed. Original SEQ ID NO: 1 has been renumbered as new SEQ ID NO: 5 and amended to incorporate the complete sequence of the Db1 cDNA in GenBank/X12556 which was disclosed on page 4, lines 10-13, of the original specification. SEQ ID NO: 6 has been added, and it recites the complete amino acid sequence encoded by new SEQ ID NO: 5. SEQ ID NOS: 4 and 5 in the original Sequence Listing have been renumbered as SEQ ID NOS: 3 and 4, respectively, in the revised Sequence Listing. Part of the original SEQ ID NO: 1 and the complete sequences of original SEQ ID NOS: 2 and 3 have been incorporated into a new SEQ ID NO: 1 which reflect the teachings set forth on pages 3 and 4 of the specification.

Specifically, on page 4, lines 14-21, of the specification, it states that "*...this Db1 gene transcribes the mRNA encoding the cDNA for which the sequence of the 2679th to 2952nd bases is represented in SEQ ID NO: 1, while in the cDNA of the variant gene, the sequence of the 3' side of the 241st base in SEQ ID NO: 1 is linked to the downstream side of the 18th base to induce a frame shift in amino acid translation, causing the 19th to 274th base in SEQ ID NO: 1 to be substituted by the sequence shown in SEQ ID NO: 2*". Please note that the SEQ ID NOS: in the above recited passage is referring of the SEQ ID NOS as originally presented in the original Sequence Listing.

As disclosed on page 4, lines 10-13, of the specification, the protooncogene Db1 cDNA is known (see GenBank Accession No. X12556 enclosed herewith). The original SEQ ID NO: 1

corresponds to the 2679th to 2952nd base of the known Db1 cDNA. New SEQ ID NO: 1 shows the entire sequence of the mutant Db1 cDNA taught in the specification. Specifically, the 1st to 2696th bases of the new SEQ ID NO: 1 is identical to the corresponding bases in GenBank/X12556 (now new SEQ ID NO: 5). By linking the 18th base ("gaa") in the original SEQ ID NO: 1 (i.e. the 2696th base of the normal Db1 cDNA (GenBank/X12556, now new SEQ ID NO: 5)) to the 242nd base ("aga") (i.e. the 2920th base of the normal Db1 cDNA) gives the 2679th to 2757th bases of the new SEQ ID NO: 1, which is described on page 4, lines 20-21, of the original specification as a sequence wherein the 19th to 274th base in the original SEQ ID NO: 1 is substituted by the sequence shown in the original SEQ ID NO: 2.

As a result of the above changes, original SEQ ID NOS: 2 and 3 have been omitted in the revised Sequence Listing. Instead, new SEQ ID NO: 2 now recites the mutant protein encoded by the mutant Db1 cDNA of new SEQ ID NO: 1.

Applicants believe that the above explanation clearly describe how the original specification support the changes in the revised Sequence Listing. However, the Examiner is invited to contact the Applicants' undersigned representative for any additional explanation if needed.

Applicants have also submitted another copy of Figure 1 as per the Examiner's request. This copy of Figure 1 is identical to the Figure 1 of the PCT Application which was transmitted by the International Bureau upon the commencement of the present national stage application.

The specification has been carefully reviewed and editorial changes have been effected. Specifically, the specification headings have been amended in conformance with U.S. practice.

Further, the specification has also been amended to correspond with the changes in the claims and in the enclosed and above described revised Sequence Listing. Support for the changes is readily apparent from the teachings of the original specification and Sequence Listing. Specific support can be found on pages 3 and 4 of the specification and SEQ ID NOS: 1-3 of the original Sequence Listing.

Claims 2 and 9 have been cancelled without prejudice. Further, claims 1 and 3 have been amended to more particularly recite the present invention and to correspond with the changes in the revised Sequence Listing. In addition, claim 7 has been amended for possible rejoinder under *In re Ochiai* and *In re Brower*, and claim 11 has been amended to clarify the claimed subject matter. Support for the claim amendments and new claims is readily apparent from the teachings of the original and amended specification and original claims.

Specifically, claim 1 has been amended to direct to *a cDNA of a disease gene for rheumatoid arthritis, which comprises the base sequence of SEQ ID NO: 1*. Further, claim 3 has been amended to direct to *a DNA fragment which comprises the base sequence of* ***a part of SEQ ID NO: 1, and necessarily contains*** *the base sequence from 2693rd to 2702nd of SEQ ID NO: 1*. The amendments to claim 3 clarifies that the claimed DNA fragment comprises not only a part of SEQ ID NO: 1, but also the base sequence from 2693rd to 2702nd of SEQ ID NO: 1.

With regard to the rejections of claims 1-3 and 9 under 35 USC § 112, first and second paragraphs, these rejections have been overcome by the cancellation of claims 2 and 9, and the amendments to the claims.

As noted above, the claims are now directed to new SEQ ID NO: 1 or part(s) thereof which the Applicants have clearly demonstrated to be in possession of at the time of the filing of the application. It should also be noted that the Examiner on page 4, line 6-8, of the April 24, 2002 Official Action agree with such a conclusion. Thus, the rejection under 35 USC § 112, first paragraph, cannot be sustained and should be withdrawn.

Further, since the claims have been clarified to direct to new SEQ ID NO: 1 or part(s) thereof, the rejection under 35 USC § 112, second paragraph, also cannot be sustained and should be withdrawn.

With regard to the rejection of claims 3 and 9 under 35 USC § 102(b) as being anticipated by Gewirtz (USP 5,612,212), this rejection has been overcome by the cancellation of claim 9 and the amendments to claim 3.

To constitute anticipation of the claimed invention, a single prior art reference must disclose each and every material element of the claim. Here, in this case, Gewirtz fails to teach or suggest a DNA fragment which comprises the base sequence of ***a part of SEQ ID NO: 1***, and necessarily contains the base sequence from 2693rd to 2702nd of SEQ ID NO: 1.

In SEQ ID NO: 7 of Gewirtz, the base sequence includes "atgaagacct", which is a partial base sequence (from 2693rd to 2702nd) of SEQ ID NO: 1 of the present invention. However, newly amended claim 3 also requires an additional part of SEQ ID NO: 1 not present in Gewirtz in addition to the base sequence of 2693rd to 2702nd of SEQ ID NO:1.

Thus, it is clear from the above that newly amended claim 3 is distinguishable and not anticipated by Gewirtz.

With regard to the rejection of claims 1-3 and 9 under 35 USC § 102(a) as being anticipated by Kamai et al. (Arthritis and Rheumatism (Sept 1999) 42 (9 supplement) page S392; for meeting held Tuesday November 16, 1999), this rejection has been overcome by the filing of the verified English translation of the certified priority document enclosed herewith. As a result of this submission, Applicants is now entitled to the foreign priority date of March 20, 1999, which antedates the earliest date (i.e. September, 1999) of the Kamai et al. reference. Thus, since Kamai et al. is no longer a valid prior art reference under 35 USC § 102(a), this rejection cannot be susttained and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the

prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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